Factor Bleeding

Introduction

Factor bleeding is **deep bleeding**, macrohemorrhages into muscle (**hematoma**) or joints (**hemarthrosis**), and is caused by a defect of **secondary hemostasis**, of the clotting cascade. When a patient is seen with major bleeding, the complete blood count assesses for platelet number and the coagulation panel assesses the PT and the PTT. But because we have separated platelet bleeding from factor bleeding, in this lesson on factor bleeding we do not mention platelet count or bleeding time except where absolutely necessary.

The clotting cascade comprises the intrinsic pathway (everyone else up to 12), the extrinsic pathway (factor 7), and the common pathway (1 five in 5, 2 fives in 10). The extrinsic pathway is monitored with the PT, while the intrinsic pathway is monitored by the PTT. Because both the intrinsic and extrinsic pathways terminate with the activation of the common pathway, defects of the common pathway will be reflected in both the PT and the PTT. And that is what this lesson is about—understanding where in the clotting cascade the defect is and correlating that to the coagulation panel. Diseases of the intrinsic pathway elevate the PTT, diseases of the extrinsic pathway elevate the PT, and diseases of the common pathway elevate both.

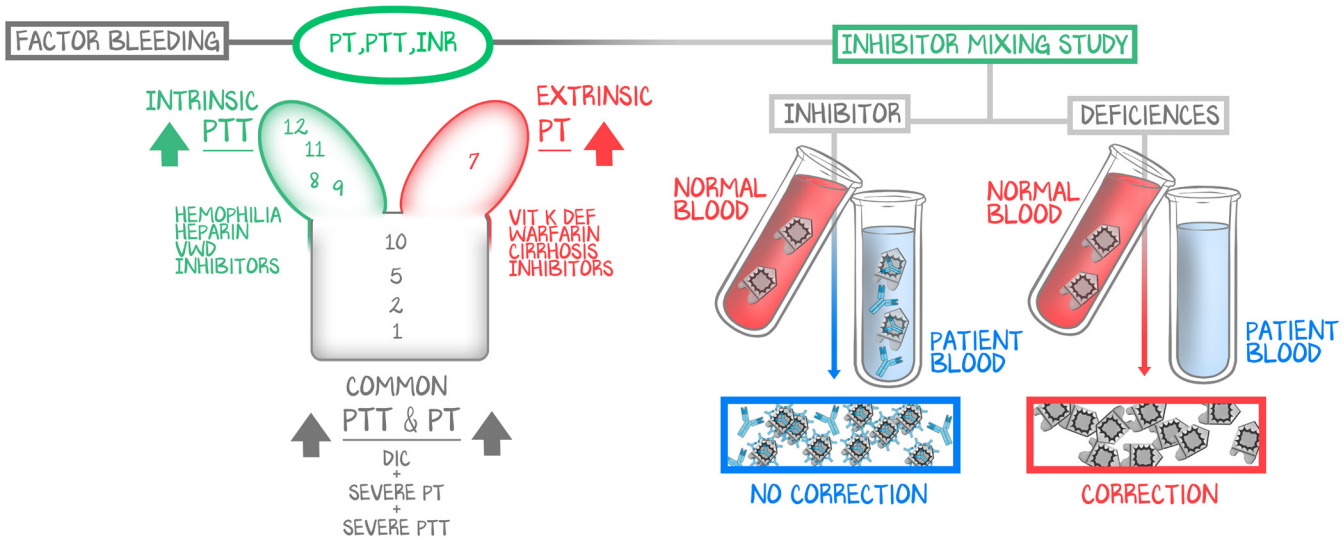

Figure 5.1: Factor Bleeding
This represents an expansion of the approach to bleeding's right arm, when the patient has deep factor bleeding. The first test to do is a PT and PTT, with a mixing study. The left side of the illustration is an advanced organizer isolating which disorders elevate the PT, the PTT, or both. The right side of the illustration shows how a mixing study works—if inhibitor, there is no correction; if deficiency, there is correction.

Every condition in this lesson comes down to whether there are **too few factors** (deficiency in production or increased inactivation) or **factor inhibitors** (antibodies against specific factors). Factor inhibitors form in patients with severe hemoglobinopathies, hemolytic anemia, or bleeding diathesis that require **lifelong blood transfusions**. This increase in exposure of foreign antigens to the immune system can precipitate antibody formation against certain factors. Factor inhibitors may also be a product of malignancy. To determine whether there is a deficiency or an inhibitor, we perform a **mixing study**. Mixing studies are performed on the blood of a patient with an elevated PT or PTT. The patient's blood sample is mixed with a sample of normal blood. If there were simply a deficiency of factor in the patient's blood, the presence of the factors in normal blood would reverse the defect. If there were antibodies against factor, and the patient's blood had the factor but its action was inhibited by the antibody, additional factor would only be bound up by the inhibitor antibodies, and the defect would not reverse.

Causes of Elevation of Only the PT

PT elevation is caused by defects in the extrinsic pathway, which consists only of factor 7. Factor 7 is one of the factors synthesized by the liver—2, 7, 9, and 10. These factors are γ-carboxylated by **vitamin K epoxide reductase** in the liver. Vitamin K epoxide reductase requires vitamin K as a cofactor. Vitamin K is a **fat-soluble vitamin** that is made absorbable by bacteria in our gut. Therefore, vitamin K requires an intact pancreas (lipase), an intact gallbladder (bile for micelle formation) and an intact ileum (fat absorption). All of the conditions that cause an elevation of the PT are in some way related to vitamin K or vitamin K epoxide reductase. Even though the liver synthesizes factors 2 and 10 of the common pathway and factor 9 of the intrinsic pathway, liver dysfunction/vitamin K deficiency/inhibition of vitamin K epoxide reductase is felt through the effects of factor 7. Until factor deficiency becomes severe, **only the PT will elevate.**

Vitamin K deficiency. Vitamin K is a **fat-soluble vitamin** (A, D, E, and K) found in **dark leafy greens**. Vitamin K deficiency, then, arises in patients with fat malabsorption or who go a prolonged time without access to nutritional vitamin K. **Fat malabsorption** occurs in a number of medical diseases (Crohn's terminal ileum inflammation or resection, chronic pancreatitis and absent lipase), pharmacologic intervention (bile acid resins), and even some infections (*Giardia lamblia*). **Deficient nutrition** is commonly seen on board exams in those individuals who consume all of their calories in the form of alcohol (homeless alcoholics). In life, however, few patients who are able to free-feed develop vitamin K deficiency. Instead, it is those patients who are unable to ask for food who are at greatest risk. **Prolonged ICU admissions** in the **elderly** are those at highest risk—intubation and ventilation for severe disease may force the patient to be NPO for days. **Newborns**, whose GI tracts have yet to be appropriately colonized with bacteria, are at highest risk for vitamin K deficiency. **Vitamin K injections** are routine in post-delivery care to prevent hemorrhagic complications of a relative vitamin K deficiency. And therein lies the treatment—if a patient is unable to ingest vitamin K or is unable to absorb vitamin K from the gut, the treatment is **intramuscular vitamin K**. Never give vitamin K intravenously; the effects are not fast enough to warrant intravenous injection and intravenous vitamin K can induce anaphylaxis.

Warfarin. Warfarin inhibits vitamin K epoxide reductase, which has the same outcome as vitamin K deficiency—a decrease in 2, 7, 9, and 10—and is monitored with the PT. Vitamin K is the antidote to warfarin toxicity.

Cirrhosis. In cirrhosis, where the hepatocytes are replaced by fibrosis, insufficient hepatocytes remain to sustain the production of factors. The levels of 2, 7, 9, and 10 are reduced. Indeed, one of the cirrhosis labs used to calculate the MELD (the severity of cirrhosis and a prognostic calculator) is the INR. The INR, in turn, is an internationally adjusted value of the PT.

Factor inhibitors and genetic defects of factor 7 would cause an elevation of the PT. These are rare, and generally are not seen. Learn them as not-a-diagnosis-you-should-consider.

Causes of Elevation of Only the PTT

PTT measures the intrinsic pathway, which involves factors 12, 11, (skip 10), 9, and 8. Deficiency of any of these factors or inhibitor antibodies against any of these antibodies will result in an elevation of the PTT.

Hemophilia describes the genetically inherited deficiency of factors of the intrinsic pathway. Hemophilia A is a deficiency of factor 8 (hemophilia "ay" for factor "ayeight"), while hemophilia B is a deficiency of factor 9 (B follows A, 9 follows eight). Hemophilia A and B are both **X-linked** recessive diseases. Hemophilia C (one that rarely gets talked about) is a deficiency of factor 11, and is **autosomal** recessive. Children present with hemarthrosis or hematomas early in life. The only thing that can be

done for them is to give **factor concentrate** for their specific factor deficiency. But because factors are short-lived, they can only be administered during times of hemorrhage. Hemophiliacs may also need blood transfusion because of the blood loss.

Heparin is monitored by following either the PTT or the 10a levels. Heparin induces antithrombin to inhibit activated factor 10 and activated factor 2. Heparin affects the common pathway, so should elevate both the PT and the PTT. Fortunately, the boards love to test that warfarin is PT and heparin is PTT, and since warfarin/PT makes sense, you just have to know that heparin is PTT. Heparin does not elevate the PT because the PT test includes heparin inhibitors. The way the procedure and materials are designed prevents the rise in the PT.

VWD presents with platelet bleeding because of insufficient VWF, and therefore the inability to adhere the platelet to the endothelial injury. VWF also stabilizes factor 8. With a relative deficiency of factor 8, the PT is elevated in VWD. It is the most commonly inherited disorder of bleeding, and is mostly mild. Because VWF can cause both a platelet bleeding and an elevated PT, it makes for nice board fodder. Look for platelet bleeding (gingival, vaginal) and an elevated PTT.

Causes of Elevations of Both PT and PTT

When **severe enough**, any condition that raises only the PT can be found to raise the PTT as well, and vice versa. So **severe** vitamin K deficiency, **severe** cirrhosis, **severe** factor deficiency, **severe** inhibitors, or **severe** heparin toxicity can also present with an elevation of both the PT and the PTT.

The main condition that will increase both consistently is the same one that is also a disorder of platelets—**disseminated intravascular coagulation**, which was discussed in the last lesson (Clotting #4: *Platelet Bleeding*).